REMARKS

Elections/Restrictions

Applicant acknowledges Examiner's decision to withdraw the election requirement of October 01, 2002.

Rejection of claims 1, 10, 16, 17 and 20 under 35 USC 102

The above-listed claims were rejected under 35 USC 102 (b) as being anticipated by Li & Baranov (U.S. Pat. No. 5,830,177). The Li patent was cited by the Examiner for teaching "compositions and treatment methods for the prevention of hair loss during chemotherapy. In a preferred embodiment, a nucleic acid comprising an expression vector capable of expressing human p-glycoprotein is administered to a subject (See Column 4, Lines 39-62). Methods of administration include the use of various carriers and incorporation into liposomes (See Column 5, Lines 16-23). Other methods of administration also include the utilization of electromagnetic radiation, including infrared radiation (See Column 5, Lines 58-66)".

Applicant respectfully submits that the Li patent does not teach compositions and treatment methods for the prevention of hair loss during chemotherapy. Instead, it teaches mechanical methods for improving the delivery of an agent to hair follicles, which methods involve the application of low-frequency vibration to the skin during or subsequent to the administration of an active agent. See independent claims 1 and 13. The mechanical vibration is designed to induce "mechanical shifts in different directions of skin structure without damage to the hair follicle". Column 2, Lines 42-44. The methods described in Applicant's patent application involve topical administration of a chemical inducer of the stress protein response or administration of an effective heat dose sufficiently prior to chemotherapy treatment. The Li patent does not describe this invention.

Examiner recounts a preferred embodiment of the invention described by the Li patent that consists of administration to a subject of a nucleic acid comprising an expression vector capable of expressing human p-glycoprotein (See Column 4, Lines 39-62). Applicant's invention does not comprise administration of a human p-glycoprotein gene. As also discussed below in response to Examiner's specific request, one

embodiment of Applicant's invention comprises administration of a gene for an activated heat shock factor 1 (HSF1). HSF1 is not identical with p-glycoprotein. HSF1 is a regulated transcription factor that mediates up-regulation of stress proteins during periods of stress. Stress proteins include major chaperone families Hsp90, Hsp70 and Hsp25 as well as other proteins such as p-glycoprotein. Hence, HSF1 is a factor that can activate the stress protein response. P-glycoprotein is merely one of several stress proteins. Its expression does not activate the stress protein response. Hence, Li's preferred embodiment is not an embodiment of Applicant's invention.

Examiner further states that "methods of administration" discussed in the Li patent "include the use of various carriers and incorporation into liposomes". While it is correct that certain embodiments of Applicant's invention make use of liposomes to administer compounds capable of inducing the stress response, Applicant fails to understand the relevance of Examiner's statement. The statement does not describe Applicant's inventive method to prevent chemotherapy-induced alopecia, which method comprises topical administration of a chemical inducer of the stress protein response or of an effective heat dose sufficiently prior to chemotherapy. Therefore, Applicant respectfully submits that Examiner's statement is not pertinent to a rejection under 35 USC 102 (b).

Examiner further asserts that Li's patent claims "other methods of administration (that) also include the utilization of electromagnetic radiation, including infrared radiation (See Column 5, Lines 58-66)". Examiner is kindly referred to the explanation appearing in Column 5, Lines 37-44 of the Li patent: "The methods and apparatuses of the present invention are particularly useful in delivering photosensitizing, photoreactive and photoactivated agents into hair follicles and the subsequent use of electromagnetic irradiation to activate that compound (hereinafter all such photo-enhanced agents will be referred to as photosensitizing agents). Specifically, following or during administration of such an agent and vibration, irradiation is applied to the treated surface". Thus, as this passage clearly explains, the method described comprises administration of a photosensitizing agent to the skin to be followed by low-frequency mechanical vibration to enhance penetration of the agent and electromagnetic irradiation to activate the photosensitizing agent. Applicant wishes to point out that this method bears no

relationship to its invention. Applicant's invention relates to the topical administration of a chemical inducer of the stress protein response or of an effective heat dose sufficiently prior to the administration of a chemotherapeutic drug. Based on these explanations, Applicant respectfully requests Examiner to withdraw his rejections under 35 USC 102 (b). Although the above arguments stand by themselves, Examiner's attention may be further drawn to the pronouncements appearing in Column 6, Lines 4-8 of the Li patent: "The choice of the photosensitizing agent will be based on the desired effect. In general, the methods will be used to ablate hair follicles for the subsequent repression of unwanted hair growth. Accordingly, photosensitizing agents that kill surrounding cells are preferred." Hence, Li's use of photosensitizing agents is to kill hair follicles, not to save them from being killed during chemotherapy.

Rejection of all claims under 35 USC 103 (a)

All claims were rejected under 35 USC 103 (a) as being unpatentable over Li & Baranov in view of Jimenez & Junis. As discussed above, the Li patent relates to a method of enhancement of penetration of an agent into hair follicles involving mechanical vibration of the skin during or subsequent to the administration of the agent. The Jimenez patent describes a method for reducing chemotherapy-induced alopecia comprising the administration of vitamin D3 or of metabolites of this vitamin, or of certain proteinaceous growth factors prior to the chemotherapy. Applicant's invention relates to the topical administration of a chemical inducer of the stress protein response or an effective heat dose sufficiently prior to the administration of a chemotherapeutic drug. Neither the Li patent, the Jimenez patent or the combination thereof suggests a method of prevention of chemotherapy-induced alopecia that is mediated by chemical or physical inducers of the stress protein response. Hence, neither patent nor the combination thereof can provide a rational basis for an obvious-type rejection. Applicant therefore respectfully requests the Examiner to withdraw his obviousness-type rejections.

Examiner further states that he "does not see a patentable distinction between the applicant's selection of an activated HSF1 in nucleic acid or protein form and disclosure in Li *et al.* of the administration of a nucleic acid comprising an expression vector capable of expressing human p-glycoprotein". Applicant respectfully submits the

following remarks: (1) Examiner's statement does not relate to all claims as is implied by its placement among other arguments for the rejection of all claims under 35 USC 103 (a). At most, the statement may relate to a single member of the Markush group recited in dependent claims 2, 4, 7, 9, 13, 15, 17 and 22. (2) Applicant's invention does not claim the use of an expression construct for p-glycoprotein. Hence, its method is readily distinguishable from any method comprising the use of such an expression vector. (3) As was also explained before, activated forms of HSF1 and p-glycoprotein are patently distinct because they are unrelated both with respect to sequence and function. Activated forms of HSF1 are mutant derivatives of specific transcription factor HSF1. HSF1 is ubiquitous and is normally inactive but is activated during conditions of stress to bind to specific sequence elements present in heat shock or stress protein genes and enhance transcription from these genes. Activated forms of HSF1 lack sequences that mediate repression of factor activity under non-stress conditions. These activated forms are therefore transactivation-competent when expressed, in contrast to the not-mutated factor. The p-glycoprotein gene was recently found to be a member of the stress protein gene group. It includes sequences that are recognized by HSF1. Hence, under stressful conditions HSF1 can bind to and activate the p-glycoprotein gene. Activated HSF1 causes enhanced expression of the entire cohort of stress proteins that include the classical stress proteins Hsp90, Hsp70, Hsp60, Hsp25 and minor proteins such as FKBP52, p32 (hemoxygenase) and p-glycoprotein. This cohort of stress proteins has multiple cytoprotective effects including inhibition of both mitochondrial and non-mitochondrial apoptotic pathways, enhancement of refolding of unfolded proteins, enhancement of disposal of misfolded proteins by the proteasomal system, as well as specific effects such as enhancement of antigen presentation, oxidation of heme or MDR1-mediated removal of drugs. In contrast, p-glycoprotein is a membrane protein that transports hydrophobic compounds including a number of compounds used in chemotherapy. The Examiner is kindly requested to take note of the fact that the Li patent neither offers any data relating to the use of and success of administering a p-glycoprotein expression construct to reduce chemotherapy-induced alopecia nor refers to any relevant publication. Hence, the patent at most invites experimentation to determine whether administration of a p-glycoprotein expression construct could be of use in

reducing chemotherapy-induced alopecia. In conclusion, Applicant respectfully submits that the mere listing of a p-glycoprotein expression vector in the Li patent neither anticipates nor obviates any of its claims.

Based on the forgoing remarks and explanations, Applicant respectfully submits that its claims 1-22 are in condition for allowance. Although this may not be directly pertinent to this response, Applicant would like to impress upon the Examiner that there is an urgent medical need for a preventive therapy of chemotherapy-induced hair loss. There are presently no effective treatments available. The medical literature is entirely devoid of descriptions of effective treatment methods that can withstand scientific scrutiny. Applicant's extensive experimentation has demonstrated the effectiveness of his therapy in an animal model. Applicant's method was found to protect with an efficacy approaching 100% against hair loss induced by some of the most widely used chemotherapeutic agents such as etoposide (VP16), cyclophosphamide (Cytoxin) and adriamycin (Doxorubicin) (in combination with cyclophosphamide).

Respectfully Submitted,

Richard Voellmy, Ph.D.

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